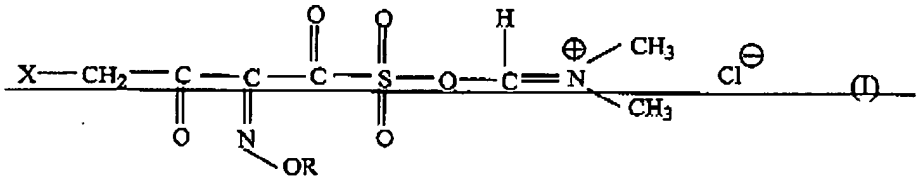
Application Number 10/540770
Response to the Office Action dated 03/20/2008

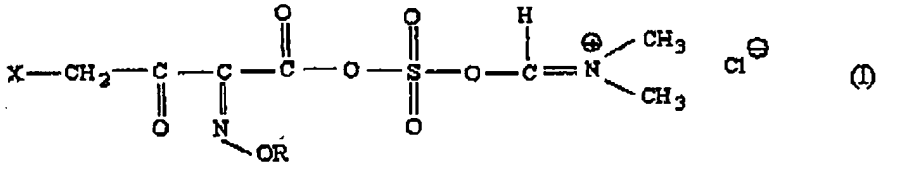
Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently Amended) A ~~novel~~ 4-halo-2-oxyimino-3-oxo butyric acid-N, N-dimethyl formiminium chloride chlorosulfate of formula (I) useful in the preparation of cephalosporin antibiotics





wherein X is chlorine or bromine;

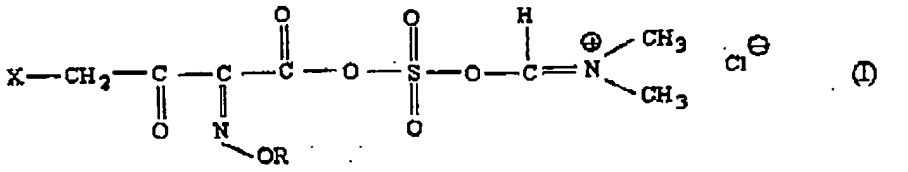
R is hydrogen, C_{1-4} alkyl group, ~~an easily removable~~ a hydroxyl protective group, selected from trialkyl silyl ethers; trialkyl aryl silyl ethers; trialkyl stannyl ethers; trityl; tetrahydropyranyl; alkyl or aryl sulphonates selected from tosyl, mesyl, and besyl; boron or aluminum containing two alkyl groups; unsubstituted benzyl; or

$-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$;

wherein R_5 is hydrogen; or ~~an easily~~ a hydrolysable ester group selected from lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxy methyl,

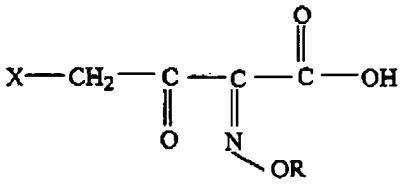
1-acetoxy ethyl, and 1-pivaloxyethyl; lower alkoxycarbonyloxyalkyl esters; alkoxymethyl esters; lower alkyl amino methyl; benzyl ester; and cyanomethyl ester.

2. (Currently Amended) A process for preparation of compound of formula (I)



(I)

comprising reacting 4-halo-2-oxyimino-3-oxobutyric acid of formula (IV^1),



(IV^1)

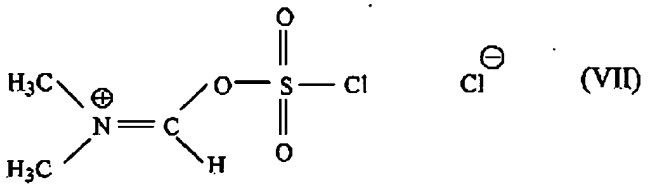
wherein X is chlorine or bromine;

R is hydrogen, C_{1-4} alkyl group, ~~an easily removable~~ a hydroxyl protective group~~,~~ selected from trialkyl silyl ethers; trialkyl aryl silyl ethers; trialkyl stannyl ethers; trityl; tetrahydropyranyl; alkyl or aryl sulphonates selected from tosyl, mesyl, and besyl; boron or aluminum containing two alkyl groups; unsubstituted benzyl; or

$-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$

wherein R_5 is hydrogen; or ~~an easily~~ a hydrolysable ester group selected from lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxy methyl, 1-acetoxy ethyl, and 1-pivaloxyethyl; lower alkoxycarbonyloxyalkyl esters; alkoxymethyl esters; lower alkyl amino methyl; benzyl ester; and cyanomethyl ester[[.]]

with N, N-dimethylformiminium chloride chlorosulphate of formula (VII)



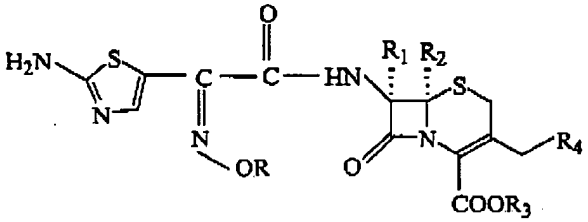
(VII)

in an organic solvent at a temperature ranging from -30^0 C to -15^0 C.

3. (Currently Amended) ~~A~~The process according to Claim 2, wherein the organic solvent is ~~selected from~~ chlorinated solvents ~~such as~~ selected from dichloromethane, dichloroethane, ~~or~~ and chloroform; aromatic hydrocarbons ~~such as~~ selected from benzene ~~or~~ and toluene; and nitriles ~~such as~~ selected from acetonitrile, propionitrile ~~or~~ and butyronitrile.

4. (Currently Amended) ~~A~~The process according to Claim 2, wherein the molar ratio of compound of formula (VII) to compound of formula (IV^1) is between 1.1 to 1.3.

5. (Currently Amended) A process for preparation of a cephalosporin compound of formula (II),



(II)

wherein

R is hydrogen, C_{1-4} alkyl group, ~~an easily removable~~ a hydroxyl protective group, selected from trialkyl silyl ethers; trialkyl aryl silyl ethers; trialkyl stannyl ethers; trityl;

tetrahydropyranyl; alkyl or aryl sulphonates selected from tosyl, mesyl, and besyl; boron or aluminum containing two alkyl groups; unsubstituted benzyl; or

$-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$;

wherein R_5 is hydrogen; or ~~an easily~~ a hydrolysable ester group selected from lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxy methyl, 1-acetoxy ethyl, and 1-pivaloxyethyl; lower alkoxycarbonyloxyalkyl esters; alkoxymethyl esters; lower alkyl amino methyl; benzyl ester; and cyanomethyl ester[[.]],

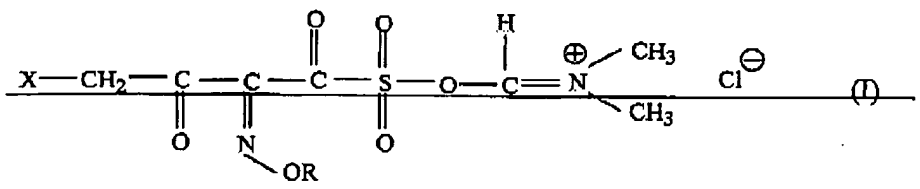
R_1 is hydrogen or [[-]]OCH_3;

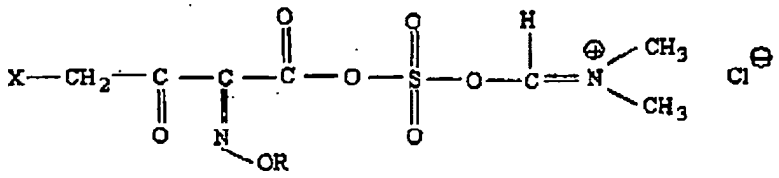
R_2 is hydrogen;

R_3 is hydrogen, a negative charge or ~~together with the COO group to which R_3 is attached is an ester, or an alkali or alkaline earth metal,~~ ester selected from the group of lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxymethyl, 1-acetoxyethyl, and 1-pivaloxyethyl ester; lower alkoxy carbonyloxyalkyl esters selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxy-ethyl ester; alkoxy methyl esters; lower alkyl aminomethyl esters; acetamidomethyl ester; benzyl ester; and cyanomethyl ester,

R_4 is hydrogen or is a substituent ~~useful in cephalosporin chemistry~~ selected from unsubstituted and substituted alkyl; and unsubstituted and substituted alkenyl; wherein substituted alkyl and/or alkenyl being substituted by alkoxy, heterocyclicthio, heterocycliccarbonylthio, alkylcarbonyloxy, or heterocyclyl;

comprising reaction of compound of formula (I)





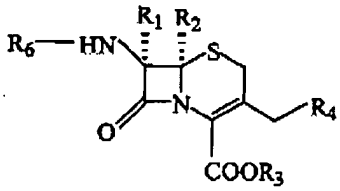
(I)

wherein X is chlorine or bromine; R and R_5 are selected from corresponding groups listed for those of formula (II) above

~~R is hydrogen, C_{1-4} alkyl group, an easily removable hydroxyl protective group, $-CH_2COOR_5$, or $-C(CH_3)_2COOR_5$~~

~~wherein R_5 is hydrogen or an easily hydrolysable ester group~~

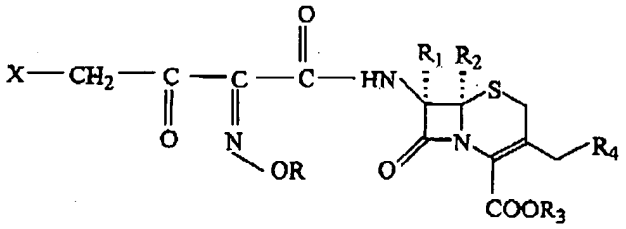
with 7-amino cephalosporanic acid of formula (V),



(V)

wherein R_1 ~~is hydrogen or $-OCH_3$;~~ and R_2 are selected from corresponding groups listed for those of formula (II) above; R_3 is selected from a group listed for R_3 of formula (II) above or a trialkyl silyl group ~~hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal, or is a silyl group~~; R_4 is selected from a group listed for R_4 of formula (II) above ~~hydrogen or is a substituent useful in cephalosporin chemistry~~; R_6 is hydrogen or a trialkyl silyl group with the proviso that, when R_3 is hydrogen, R_6 is also hydrogen; when R_3 is a trialkyl silyl group, R_6 is also a trialkyl silyl group; and when R_3 is an ester, ~~or an alkali or alkaline earth metal~~ R_6 is hydrogen

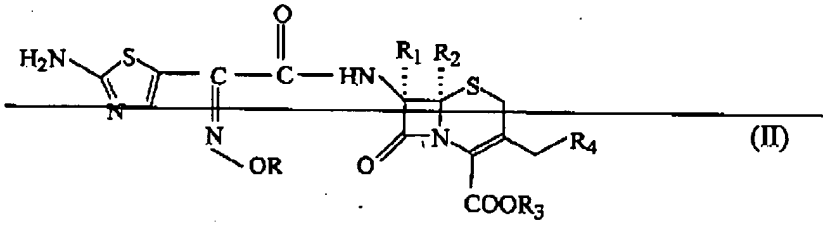
to give 7-[(4-halo-2-oxyimino-3-oxobutyramido)-3-substituted-3-cephem-4-carboxylic acid of formula (VIII),



(VIII)

wherein X, R, R_1, R_2, R_3 and R_4 ~~have~~ are corresponding groups listed for those of formula (I) or (II) above ~~the same meanings as defined hereinearlier, and R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester, or an alkali or alkaline earth metal.~~

followed by cyclisation of compound (VIII) with thiourea, ~~to give compound of formula (II),~~



(II)

~~wherein R and R_5 are as defined above; R_1 is hydrogen or OCH_3; R_2 is hydrogen; R_3 is hydrogen, a negative charge or together with the COO^- group to which R_3 is attached is an ester or an alkali or alkaline earth metal; R_4 is hydrogen or is a substituent useful in cephalosporin chemistry.~~

6. (Currently amended) ~~A~~The process according to Claim 5, wherein the reaction of compound (I) and compound (V) to give compound (VIII) is carried out in an organic

solvent and in the presence of a base at a temperature ranging from -80^0 C to -15^0 C[[,]].

7. (Currently amended) ~~A~~The process according to Claim [[5]]6, wherein the ~~the~~ organic solvent is selected from chlorinated solvents ~~such as dichloromethane, dichloroethane, and chloroform~~; aromatic hydrocarbons ~~such as benzene and toluene~~; nitrile solvents ~~such as acetonitrile, propionitrile and butyronitrile~~; and ethers ~~such as tetrahydrofuran and dioxane~~.

8. (Currently amended) ~~A~~The process according to Claim [[5]]6, wherein the base is selected from N, N dimethyl aniline, diethyl amine, and pyridine.

9. (Currently amended) ~~A~~The process according to Claim 5, wherein the molar ratio of compound (I) to the cephalosporin compound (V) is between 1.1 to 2.0~~, preferably between 1.2 to 1.5~~.

10. (Currently Amended) ~~A~~The process according to Claim 5, wherein the preferred temperature is between -55^0 C to -25^0 C.

11. (Currently Amended) ~~A~~The process according to Claim 5, wherein the reaction of compound (VIII) and thiourea to give the cephalosporin compounds of formula (II) is carried out in a mixture of organic solvent and water and in the presence of a base at low to ambient temperature.

12. (Currently Amended) ~~A~~The process according to Claim [[5]]11, wherein the ~~the~~ organic solvent is selected from chlorinated solvents ~~such as dichloromethane, dichloroethane, and chloroform~~; aromatic hydrocarbons ~~such as benzene and toluene~~;

nitrile solvents ~~such as acetonitrile, propionitrile and butyronitrile~~; and ethers ~~such as tetrahydrofuran and dioxane~~.

13. (Currently Amended) ~~A~~The process according to Claim [[5]]6, wherein the base is selected from alkali metal carbonates, such as sodium carbonate, potassium carbonate and lithium carbonate; alkali metal hydrogen carbonates, such as sodium hydrogen carbonate and potassium carbonate; and alkali metal acetates, such as sodium acetate and potassium acetate.

14. (Currently Amended) ~~A~~The process according to Claim 5, wherein ~~the~~ a temperature at which the reaction is carried out is between -5^0 C ~~to~~ and 40^0 C, ~~preferably between 10^0C to 30^0C~~.

15. (Currently Amended) ~~A~~The process according to Claim 5, wherein the compound of formula (II) is any one of

i) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefdinir,

ii) 7-[(Z)-2-(2-amino-4-thiazolyl)-2-methoxyimino)acetyl]amino-3-[(1Z)-2-(4-methyl-5-thiazolyl)ethenyl -3-cephem-4-carboxylic acid, i.e. cefditoren and the pivaloyloxymethyl ester i. e. cefditoren pivoxil,

iii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methylpyrrrolodino) methyl-3-cephem-4-carboxylate i.e. cefepime,

iv) 7-[(Z)-2-(2-aminothiazol-4-yl)methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid i.e. cefetamet, and the pivaloyloxymethyl ester i. e. cefetamet pivoxil,

v) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefixime,

vi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-methyl–1H-tetrazol-5-yl]thio]methyl]-3-cephem-4-carboxylic acid i.e. cefmenoxime,

vii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[[5-carboxymethyl)-4-methyl-2-thiazolyl]thio]methyl]- 3-cephem-4-carboxylic acid i.e. cefodizime,

viii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,3-dihydro-2-(2-hydroxyethyl)-3-imino-1H-pyrazol-1-yl]methyl]- 3-cephem-4-carboxylic acid i. e. cefoselis,

ix) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanic acid i.e. cefotaxime,

x) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[92,3-cyclopenteno-1-pyridinium)methyl]- 3-cephem-4-carboxylic acid i.e. cefpirome,

xi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate- i.e. cefpodoxime and the 1-methylethoxycarbonyloxy ether i. e. cefpodoxime proxetil,

xii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl-5,6,7-tetrahydroquinolinium-4-carboxylic acid inner salt i. e. cefquinome,

xiii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethyl)oximinoacetamido}-3-[pyridinium]methyl-3-cephem-4-carboxylacid acid inner salt i. e. ceftazidime,

xiv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(5-methyl-1,2,3,4-tetrazoyl)-methyl-3- cephem-4-carboxylic acid i. e. cefteram and the and the pivaloyloxymethyl ester i. e. cefteram pivoxil,

xv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid i. e. ceftiofur,

xvi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid i. e. ceftizoxime,

xvii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid i. e. ceftriaxone, and

xviii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-ylthio)methyl]- 3-cephem-4-carboxylic acid i. e. cefuzonam.

16. (New) The compound of formula (I) according to Claim 1, wherein R_5 is lower alkyl ester selected from methyl, ethyl, and tertiary butyl; lower alkoxycarbonyloxyalkyl ester selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, and 1-isopropoxycarbonyloxy ethyl; methoxymethyl ester; or acetamidomethyl ester.

17. (New) The process according to Claim 2, wherein R_5 is lower alkyl ester selected from methyl, ethyl, and tertiary butyl; lower alkoxycarbonyloxyalkyl ester selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, and 1-isopropoxycarbonyloxy ethyl; methoxymethyl ester; and acetamidomethyl ester.

18. (New) The process according to Claim 5, wherein R_5 is lower alkyl ester selected from methyl, ethyl, and tertiary butyl; lower alkoxycarbonyloxyalkyl ester selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, and 1-isopropoxycarbonyloxy ethyl; methoxymethyl ester; and acetamidomethyl ester.

19. (New) The process according to Claim 5, wherein R_3 is lower alkyl ester selected from methyl, ethyl and tertiary butyl; and methoxymethyl ester.

20. (New) The process according to Claim 6, wherein the organic solvent is chlorinated solvent selected from dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbon selected from benzene and toluene; nitrile solvent selected from acetonitrile, propionitrile, and butyronitrile; or ethers selected from tetrahydrofuran and dioxane.

21. (New) The process according to Claim 11, wherein the organic solvent is chlorinated solvent selected from dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbon selected from benzene and toluene; nitrile solvent selected from acetonitrile, propionitrile, and butyronitrile; or ethers selected from tetrahydrofuran and dioxane.